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10/581,034	05/30/2006	Hiromu Ohnogi	1422-0716PUS1	5993

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
SOLOLA, TAOFIQ A	
ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,034	OHNOGI ET AL.	
	Examiner	Art Unit	
	Taofiq A. Solola	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,4,5 and 8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,4,5 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This communication supersedes the previous Office action.

Claims 1-2, 4-5, 8-11 are pending in this application.

Claims 3, 6-7 are cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims lack adequate support in the specification. The term "hydrolysable prodrug" is not defined in the specification so as to ascertain the structures of the compounds that are included and/or excluded by the term. In patent examination, it is essential for claims to be precise, clear, correct, and unambiguous. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). By deleting the term the rejection would be overcome.

Claim 4 is drawn to mechanism: inhibition of aldose reductase. This is not a practical utility under the US patent practice. To ascertain the practical utilities, one must read the specification into the claims contrary to several precedent decisions by the US courts and Official practice. The claim is an attempt by applicant to claim treatment of all diseases known today and that may be discovered in the future, arising from the mechanism. It is a reach-through claim and is no longer patentable under the US patent practice. A claim must stand alone to define the invention, and incorporation into the claims by reference to the specification

or an external source is not permitted. Ex parte Fressola, 27 USPQ 2d 1608, BdPatApp & Inter. (1993). By deleting the claim the rejection would be overcome.

Claims 8-9 and are not supported by the specification, paragraph [0032], as asserted by applicant. The same is true of claims 10-11 and paragraph [0048]. By deleting the claims the rejection would be overcome.

Claims 4, 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the claimed mechanism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"'In the context of determining whether sufficient "utility as a drug, medicant, and the like in human therapy" has been alleged, It is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the [compounds and the utilities] as obviously correct." *In re Jolles*, 628 F.2d 1327, 1332 (Fed. Cir. 1980), citing *In re Novak*, 306 F.2d 924 (CCPA 1962); see 340 F.2d 974, 977-78 (CCPA 1965).

"A specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), Id. at 1566, quoting *Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Fiers v. Revel,* 984 F.2d 1164, 1171-72 (Fed. Cir. 1993), quoting *Marzocchi*, 439 F.2d at 223; see also *Armbruster*, 512 F.2d 676, 677 (CCPA 1975); *Knowlton*, 500 F.2d 566, 571 (CCPA 1974); *Bowen*, 492 F.2d 859 (CCPA 1974); *Hawkins*, 486 F.2d 569, 576 (CCPA 1973).

Where there is "no indication that one skilled in the art would accept without question [the instant compounds and method of use] and no evidence has been presented to demonstrate that the claimed products do have those effects *Novak*, 306 F.2d at 928, an applicant has failed to sufficiently demonstrate sufficient utility and therefore cannot establish enablement.'" *In re Rasmusson,* 75 USPQ2d 1297 (CAFC 2005). The claimed invention is not enabled without undue experimentation for the following reasons:

For rejection under 35 U.S.C. 112, first paragraph, the following factors must be considered. *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC, 1988): "The factors to be considered [in making an enablement rejection] have been summarized as a) the breadth of the claims, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and, the quantity of experimentation necessary, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex prate Formal*, 230 USPQ 546. The breath of the claims includes compounds 1-9. The nature of the invention is using the compounds as pharmaceuticals, in food, beverage or animal feeds. There is no known prior art that broadly teaches applicability of the compounds for treating all the listed diseases and inhibition of aldose reductase. For example, see Dimmock et al., Current Med. Chem. (1999), Vol. 6(12), pp. 1125-1149.

It is quite possible that mutations in the genes for the proteins responsible for aldose reductase may lead to increase level. To use the invention as claimed, one of ordinary skill in the art would have to perform experimentation in every instance to determine if the increase is due to genetic mutation in a patient or not. After prospective patients are identified and treated, assays must be performed on each one to determine if treatment is successful. However, the specification fails to disclose a routine procedure to perform such assay. Therefore, to make

and use the instant invention, one of ordinary skill in the art would have to perform significant amount of experimentation. Such is deemed undue experiment under the US patent practice. There are no assays in the specification to determine increased levels of aldose reductase and what normal and abnormal levels are.

Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate, is filled with experimental uncertainty.

Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria requires a large quantity of experimentation. Wolff (Medicinal Chemistry) summarizes the state of the prodrug art in Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed.

Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol in the specification is particularly relevant. Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596, in the first sentence, third paragraph on page 596 states that “extensive development must be undertaken” to find a prodrug. Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans

making prodrugs as collaborative team of synthetic pharmaceutical chemists and metabolism experts. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The specification fails to disclose any study of the prodrugs of the instant compounds.

There is no evidence that the instant compounds would treat all categories of cancers as required under the FDA guideline, namely: carcinoma, sarcoma myeloma, leukemia, lymphoma and mixed types. Testing of any form of cancer is not performed. The claims are drawn to treatment of all inflammatory response, treating all cancers, etc. According to Matthews et al., Cancer Res. (2007), Vol. 67(6), pages 2430-2438 (www.aacrjournals.org), not only is cancer in human requires chronic exposure to a combination of tumor promoters, activating protein and nuclear factor activation are required during promotion and progression of cancers. For example, cervical cancer may be initiated by exposure to HPV (e.g. HPV16) it requires many years of promotion such as exposure to estrogen as well as exposure to HPV16-E7 oncoprotein. See Matthews et al., *Ibid.* However, the authors state that skin carcinogenesis is unique for not requiring nuclear activation.

The "fact that [the] art of cancer chemotherapy is highly unpredictable places on drug patent applicants to provide basis for believing speculative statements placed in the specification as positive assertion are true, and failing such, ignorance of PTO in not being able to provide scientific reason why assertion is not sound is not justification for permitting assertion to be made, where those of ordinary skill in the art would not accept assertions as believable without some data or other evidence to support it." *In re Hozumi,* 226 USPQ 353, (ComrPats, 1985). "Proof of utility is sufficient if it is convincing to one [of] ordinary skill in the art, amount of evidence required depends on facts of each individual case, character and amount of evidence

needed may vary, depending on whether alleged utility appears to accord with or to contravene scientific principles and beliefs." *In re Jolles,* 206 USPQ 885 (CCPA, 1980).

"[W]here application is directed toward treatment of humans, clinical case histories showing that compound is useful in the treatment of two types of cancer (in the instant case, none), do not establish utility of compounds for treatment of other kinds of cancers, such evidence, limited to one compound and types of cancers, is not commensurate with [a] broad scope of utility" of treating all forms of cancers. *In re Buting,* 163 USPQ 689 (CCPA, 1969). Even though "the state of cancer treatment has advanced remarkably, decisional law would seem to indicate that the [instantly claimed] utility is sufficiently unusual to justify an examiner's requiring substantial evidence, which may be in the form of animal tests." *Ex parte Krepelka, et al.,* 231 USPQ 746 (BdPatApp&Int, 1986).

The diseases cited on pages 12-13 of the specification, as arising from increased aldose reductase are mere speculations. There is no conclusive evidence in the specification that established nexus between the diseases and aldose reductase. There is no discussion and/or analysis of the results in tables 1-2 and no correlation is established between the results and each of the claimed utilities.

There is no disclosure on how to make the prodrugs. Therefore, to make and use the instant invention, one of ordinary skill in the art would have to perform significant amount of experimentation by trial and error. She must start from the beginning to the end of textbooks in organic chemistry to determine if any structurally close compound is in fact hydrolysable to any of the compounds. Such is deemed undue experiment under the US patent practice.

There is no absolute predictability or established correlation between the claims and the specification disclosures. The uncertainty presents one of ordinary skill in the art with obstacles and prevents her from accepting the invention on its face. Predictability in the art refers to the

ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. *See Ex parte Mass*, 9 USPQ2d 1746, (1987).

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding any of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. By deleting the claims the rejection would be overcome.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 4, 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For the reasons set forth above under 35 USC 112, first paragraph the claims are indefinite. See the Examiner's suggestions above.

The term "hydrolysable prodrug" is not defined in claims 8-9 so as to ascertain the structures of the compounds that are included and/or excluded by the term. Therefore, it is not possible to ascertain the metes and bounds of the claims.

Claims 4 improperly depends from claim 2 for failure to limit the scope of claim 2. The claims are drawn to the same agent (composition). Claim 4 cites intended uses. Under the US patent practice intended use is not a limitation of a compound or product. *In re Hack*, 114USPQ 161 (CCPA, 1957); In *re Craig*, 90 USPQ 33 (CCPA, 1951); *In re Brenner*, 82 USPQ 49 (CCPA, 1949). By deleting the claim the rejection would be overcome.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-2, 4-5, 10-11 are rejected under 35 U.S.C. 102(a) as being anticipated by Enoki et al., WO 2004/096198.

Enoki et al., disclose compound Ka9, and its composition for treating diabetic related diseases.

Claim 1-2, 4-5, 8-11 are rejected under 35 U.S.C. 102(a) as being anticipated by JP 64-13019.

According to the ISR and Written Opinion of PCT/JP2004/017887, the instant compounds, compositions and utilities thereof, are not patentable over JP 64-13019. However, the Office will revisit this rejection when an English translated copy is filed. The full document, in English or otherwise, is not currently filed.

Claim 8-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohnogi et al., WO 2001/54682.

Ohnogi et al., disclose compounds 26, 27, their compositions and methods of use, which are ether and hydrolysable prodrugs of the instant compounds absent a showing to the contrary.

Response to Argument

Applicant's arguments filed 12/20/07 have been fully considered but they are not persuasive. Applicant argues that many diseases relating to abnormal NO production are well

known, citing US 2003/0040541 and US 5.635,505, on support thereof. This is not persuasive because the documents are not incorporated by reference in accordance with the MPEP 608.01, and the requirement of 35 USC 112, is not what is known or obvious to one of ordinary skill in the art but a "full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same", *Lookwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed Cir. 1997). See also the status above.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola, PhD. JD., whose telephone number is (571) 272-0709. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

/Taofiq A. Solola/

Primary Examiner, 1625

March 18, 2008